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# Zinc supplements and bone health: The role of the RANKL-RANK axis as a therapeutic target

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ABSTRACT

*Background:* To this day, empirical data suggests that zinc has important roles in matrix synthesis, bone turnover, and mineralization and its beneficial effects on bone could be mediated through different mechanisms. The influence of zinc on bone turnover could be facilitated via regulating RANKL/RANK/OPG pathway in bone tissue. Therefore, the aim of the study was to conduct a review to investigate the possible effect of the zinc mediated bone remodeling via RANKL/RANK/OPG pathway.

*Methods:* A comprehensive systematic search was performed in MEDLINE/PubMed, Cochrane Library, SCOPUS, and Google Scholar to explore the studies investigating the effect of zinc as a bone remodeling factor via RANKL/RANK/OPG pathway regulation. Subsequently, the details of the pathway and the impact of zinc supplements on RANKL/RANK/OPG pathway regulation were discussed.

*Results:* The pathway could play an important role in bone remodeling and any imbalance between RANKL/RANK/OPG components could lead to extreme bone resorption. Although the outcomes of some studies are equivocal, it is evident that zinc possesses protective properties against bone loss by regulating the RANKL/RANK/OPG pathway. There are several experiments where zinc supplementation resulted in upregulation of OPG expression or decreases RANKL level. However, the results of some studies oppose this.

*Conclusion:* It is likely that sufficient zinc intake will elicit positive effects on bone health by RANKL/RANK/OPG regulation. Although the outcomes of a few studies are equivocal, it seems that zinc can exert the protective properties against bone loss by suppressing osteoclastogenesis via downregulation of RANKL/RANK. Additionally, there are several experiments where zinc supplementation resulted in upregulation of OPG expression. However, the results of limited studies oppose this. Therefore, aside from the positive role zinc possesses in preserving bone mass, further effects of zinc in RANKL/RANK/OPG system requires further animal/human studies.

## 1. Introduction

The skeleton is responsible for enduring mechanical load in the body and plays some important roles in inflammation, hormonal and mineral challenges in the body. Further, it is suggested that the skeleton may influence the parenchymal function of organs such as the kidney and pancreas by secreting some agents [1]. As a connective tissue, the skeleton has 4 types of cells including osteoblasts, osteoclasts, osteocytes, and bone lining cells. Bone tissue is perpetually in turnover; where osteoblasts control the formation of bone, and osteoclast activities lead to bones resorption [2]. Bone mass is mainly comprised of minerals in varying types and combinations, such as hydroxyapatite, proteins including collagen and noncollagenous proteins, water and etc. each of these components is influencing by gender, disease, age, and site [3]. There are many risk factors that may deleteriously impact skeleton health, including low calcium level, vitamin D deficiency, sedentary lifestyle, hyperthyroid and hypothyroid, high blood pressure, high-stress level, hysterectomy, and postmenopause [4]. Some of the disorders that mainly involve the skeleton include osteoporosis, rickets, osteomalacia, renal osteodystrophy, Paget's disease and malignancy of bone [5]. When bone mass reduced, some harmful change appear in bone structure [6]. Further, bone health is weakened as people age, especially in developing countries [7]. In Britain, 1 in 5 men and 1 in 2 women over fifty years old, suffer from at least one fracture during their lifetime [8]. Based on recent findings, over 200 million people suffer from osteoporosis, globally [9], with most fractures occurring in the hips and forearm [10]. Although the actual effects of pharmacological agents on bone disorders is not yet clear; there is a burgeoning field of

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research dedicated to elucidating potential interactions. Some of the most common drugs in bone diseases include bisphosphonates, denosumab, estrogen, PTH peptide, Strontium ranelate, DKK1, and sclerostin antibodies, and calcium-sensing receptor antagonists [11]. On the other side, there are some medications that may have negative influences on bone health, including thyroid medications [12], anti-diabetic drugs [13], proton pump inhibitors [14], and antidepressants [15]. In order to preserve bone health, sufficient and persistent intake of some nutrients such as vitamin D, vitamin K, vitamin A, calcium, magnesium, fluoride, phosphorus, copper, potassium and zinc are necessary [16]. With a proper nutritional strategy, it is conceivable that reductions in bone loss, especially at early ages when the genome still has time for epigenetic changing, maybe feasible [7].

Zinc is one of the important minerals for growth and bone health preservation; whilst deficiency in zinc has multiple complications, including diarrhea, alopecia immune dysfunction, growth retardation, and cognitive impairment. Aging, bone resorption and post-menopause all act to reduce zinc quantities in bone [17–19]. Zinc is required for protein and DNA synthesis in the skeleton [20,21], whilst zinc deficiency leads to a major reduction in collagen synthesis and turnover [21]. It is also a stimulant for osteoblastic cells and suppresses osteoclast activity [22]. Empirical data suggests that zinc has important roles in matrix synthesis, mammalian system and probably in bone mineralization [23], and its protective and beneficial effects on bone could be mediated through cell proliferation, increasing collagen production, and stimulation alkaline phosphatase activity [24]. Furthermore, influence on bone turnover could be facilitated via zinc regulating RANKL/RANK/OPG pathway in bone tissue [25]. Zinc could inhibit the osteoclastogenesis which is induced by RANKL (receptor activator of NF-KB ligand) [19]. The pathway and its components are part of the tumor necrosis factor (TNF) superfamily, which could play an important role in bone remodeling. RANKL/RANK axis control osteoclasts formation and activity [26]. Moreover, these are identifying as key indicators on bone turnover in bone-related pathological situations. OPG, as the RANKL`s decoy receptor, plays a bone protective role by binding to RANKL and prevention of bone resorption [26]. The imbalance between RANKL and OPG could lead to extreme bone resorption [26].

Although, there are several studies depicting the beneficial effects of zinc on bone health; the current evidence is not enough to approve the bone protective role of zinc supplementation in respect to RANKL/RANK/OPG balance. Therefore, the aim of this study was to review the effect of zinc supplements on regulation of RANKL/RANK/OPG axis which will help the future studies to focus and assist in developing potent strategies for treating patients with bone disorders.

A comprehensive systematic search was performed in MEDLINE/PubMed, Cochrane Library, SCOPUS, and Google Scholar to explore the studies investigating the effect of zinc as a bone remodeling factor via RANKL/RANK/OPG pathway regulation. We comprehensively searched through the databases for in vitro and in vivo studies that investigated the effect of zinc on bone health via regulation of RANKL/RANK/OPG pathway. Additionally, we tried to find more related studies with manual reference list checking. We used both MeSH term and free-text in titles/abstracts as follow: ("Zinc"[Mesh] OR “Zinc supplement*”) AND (“"Bone and Bones"[Mesh]) AND ("RANK Ligand"[Mesh] OR “RANKL” OR “RANK” OR “Osteoprotegrin” OR “OPG”. We did not restrict the searches according to their languages or the type of study. The studies for literature review were selected if they met the following criteria: 1) using any form of zinc as single or multi-component supplement, 2) studies in which they investigated the role of zinc in RANKL/RANK/OPG modulation regarding the bone cells. We primarily searched and identified the eligible in-vivo and in-vitro studies by electronic searching and manual searching of reference lists of eligible studies. By secondary screening, ineligible articles were excluded due to duplication in investigated databases, and being irrelevant to the purpose of the current review. Subsequently, the details of the pathway and the impact of zinc supplements on RANKL/RANK/OPG pathway regulation were discussed.

## 2. Zinc and bone health

There are multiple trace minerals which participate in bone metabolism, such as copper, magnesium, fluoride, and zinc [27]. Low level of copper and magnesium in serum can lead to depletion in BMD [28,29]. Zinc is one of the most essential trace elements for the body [30], is an important cofactor for DNA and RNA synthesize enzymes, and is a major stimulant for growth [31], and could interfere in chemical catalysis or indirectly participate in protection of protein structure [32]. Zinc food sources include; red meat, poultry, shellfish, seeds, nuts, dairy, and beans [33], and a reported 2 billion people suffer from zinc deficiency, necessitating supplementation with zinc [34]. Zinc supplements have varying side effects and different absorption rates based on their composition, with zinc sulfate, zinc picolinate, zinc acetate, zinc gluconate, zinc orotate, and zinc citrate are available zin supplements in market [35–37]. Zinc deficiency can result in, for example, alopecia, dermatitis, loss of appetite, immune system dysfunction, and growth retardation [38,39]. Conversely, zinc toxicity includes issues such as nausea, vomiting, lethargy, fatigue and epigastric pain [40]. There is about 2–3 gr zinc in the human body and approximately 0.1% of this amount is excreted which and thus must be replenished through dietary intake [31]. A great amount of total body zinc esides in the skeleton [41]. It has been shown that zinc has an essential role in bone metabolism and mineralization, for instance, in osteoblasts, zinc could activate aminoacyl-tRNA synthetase and also prohibit osteoclasts from bone resorption. Zinc increases protein synthetase which helps in the protection of bone health [42]. It has been suggested that urinary zinc level may be employed as a convenient marker for bone loss recognition [43]. Zinc could result in significant upregulation in alkaline phosphatase activity which is important for bone calcification and plays an important role as a biochemical marker for bone development [44,45], zinc finger transcription factors, TRAF6-inhibitory zinc finger protein and Schnurri-3 [46]. Aging, bone unloading and post-menopause may facilitate a reduction in bone zinc quantities [25]. Since almost 800 μg per gram of creatinine is expelled in urine in women with osteoporosis, urinary zinc is utilized as a marker for bone resorption in postmenopausal women [47]. It has been shown that zinc receptors are necessary for the normal matrix and cells in bone. Antecedent work has indicated that zinc and its receptor could change the expression of some enzymes and adjust collagen production in the skeleton [48]. Furthermore, zinc activity in the bone could affect both proliferation and differentiation of osteoblast-like cells [49]. Oral intake of zinc supplements could help to protect bone from resorption in various conditions, such as aluminum toxicity, Ca deficiency, vitamin D deficiency, estrogen deficiency, diabetes, and arthritis. So, administration of zinc compounds could add to bone loss protection and prevention protocols [50]. Zinc deficiency contributes to many types of abnormalities in bones in fetal and postnatal terms [50]. In young animals, where zinc deficiency is identified, they face to reduction in somatomedin (IGF-I) synthesis and growth problem [51,52]. A zinc finger transcription factor, Osterix (Osx), is expressed in, almost, all growing bones; the genetical role of Osx in bone formation and bone homeostasis is well known and operates gene collection for differentiation of pre-osteoblasts to osteoblasts and osteocytes [53]. Zinc chelated with β-alanyl-L-histidine results in the formation of β-Alanyl-L-histidine zinc (AHZ), which can stimulate bone formation more than zinc sulfate. In addition, zinc acexamate is another compound which has identical effects to AHZ in bone formation, and is comparable with other bone regulator factors [25]. Some studies indicate zinc may elicit positive influences on the healing of bone fractures [54,55]. The ability of zinc to suppress osteoclastogenesis is likely because of its inhibitory effects on RANKL. Moreover, it may conceivably prevent the pre-osteoclast signaling pathway which is related to the RANK/RANKL system [50].

## 3. RANKL/RANK/OPG pathway

Nf-kB is a superfamily, where constituent proteins take part in the signaling pathways [56]. Some of the Nf-kB family members are controlled in inflammatory and neoplastic conditions that might be motivated by proinflammatory factors [57]. Also, elimination of some of these agents may leads to unwanted bone development [58]. One of the most important systems of this family is RANKL/RANK/OPG signaling pathway, is regarded an important system for immunity and is essential for bone homeostasis [59]. RANK or receptor activator of NF-kB is a transmembrane protein contain 3 subunits. It originally discovered in mature osteoblasts, dendric cells and osteoclast precursors (OCP) [60]. A deletion mutation in RANK which reported in transgenic mice identified the significance of RANK in osteoclastogenesis [61]. RANKL (receptor activator of NF-kB ligand also known as osteoclast differentiation factor) is a homotrimeric protein, part of TNF superfamily, and is encoded by TNFSF11 gene [61]. RANKL is mainly expressed by activated T cells, osteoblasts, fibroblasts and stromal cells [62], and expressed in mammary gland epithelial cells during pregnancy, causing hyperplasia during lactation [63]; in addition, it is expressed in some tumor cells and may control their proliferation [64]. Overexpression of RANKL has been observed in various diseases such as arthritis rheumatoid and psoriatic arthritis [65,66]. RANKL is regulatable by different agents such as glucocorticoids, TNF-a, TGF-b, IL-1 LSP. this protein has the facility to bind to both RANK and OPG [59]. OPG (the soluble decoy receptor osteoprotegerin) encoded by TNF receptor family member 11B gene (TNFRSF11B) [67], and has been detected during an investigation designed for TNFR (tumor necrosis factor receptor) related molecules [68]. OPG mRNA has been found in many cell types, including skin, liver, heart, lung and bone marrow stromal cells [69,70]. The main responsibility of OPG is inhibition of RANK matching with RANKL [67]; moreover, OPG could bind to TRAIL (TNF-related apoptosis-inducing ligand) to prevent TRAIL-induced apoptosis [71]. In addition to RANKL and TRAIL, OPG could bind to some other agents like glycosaminoglycans (GAGs), von Willebrand Factor, Factor VIII-von Willebrand Factor complex, and syndecan-1 [72]. The RANKL/RANK/OPG system has important roles in various organs and conditions such as bone modeling and remodeling [61], cancer cells [73], pregnancy [63], immune system [74], and cardiovascular disease [75].

## 4. RANKL/RANK/OPG in bone

Osteoclasts are regarded the most important cells in bone resorption, where osteoclast precursors have the potential to maturate via stimulation of some factors. Among these factors, there are 2 cytokines; M-CSF, a cytokine that secreted by several types of cells like stromal cells and osteoblast, and receptor activator of NF-kB, part of RANKL/RANK/OPG system [76]. RANKL/RANK/OPG system is active in various conditions including vascular calcification [77], cancer [78], bone modeling a remodeling, and some genetic disorders [79]. The discovery of RANKL/RANK/OPG system in bone turnover in the late 1990s is regarded as an important finding for developing bone health [80].

The interaction between RANK and its ligand (RANKL), on the external layer of OPCs (osteoclast precursor cells), results in maturation of these cells and turning to osteoclasts. Osteoclasts which migrated to the bone surface, secretion of some enzyme like cathepsin K and tartrate-resistant acid phosphatase, and acceleration of bone resorption. Osteoprotegerin expressed by bone stromal cells and osteoblasts, play role as decoy receptor for RANKL and prevents the binding of RANK and RANKL with its higher affinity to RANKL [81]. The OPG-RANKL ratio is less than 1 in postmenopausal women [49], with some studies reported that blocking RANKL leads to an increase in OPG level, and could noticeably reduce bone loss during lactation [82]. The timing of RANK expression and its link to RANKL is a serious issue in osteoclastogenesis [83]. Both RANKL and RANK must be present in order for osteoclastogenesis to happen, where, in mice unable to express RANK and RANKL, they suffered from osteopetrosis [84]. However, in mice with OPG deficiency, osteoporosis occurred earlier than normal mice, attributed to the high number of osteoclasts differentiation [85]. OPG overexpression in animal models has resulted in deep osteoporosis to the extent that a total loss in osteoblasts happen [86]. Rheumatoid arthritis is an inflammatory disease that can weaken bone in numerous ways. RANKL is one of the factors that have expected to take part in RA bone problems. Suppressing RANKL and other agents like TNF represent a promising treatment for minimizing RA Complications [87]. Paget disease is another bone disorder with the Interference of RANKL-RANK in its development [88]. Paget disease of bone is mainly identified by central bone resorption and increased osteoclast activity. In PDB, RANKL expression and its sensitivity increases which leads to more bone problems [89]. Recent studies regarding bone cancer have investigated signaling systems in this disease; RANKL and RANK most probably have developing effects on bone tumors while OPG could be decreasing cancer-induced bone pain [73,90]. Tumor cells upregulating RANKL expression in bone stromal cells through increasing IL-6, IL-1B, TNF, epidermal growth factor and PTH-related peptide (PTH-rP), so osteoclastogenesis increased [91]. In this case, using the anti-RANKL treatment such as anti-RANKL medication (like denosumab) or gene therapy might have significant effects in cancer development [92]. Furthermore, recent investigations has suggested that mechanical pressure could lead osteocytes to recall osteoclasts to the bone resorption sites via regulating RANKL synthesis in osteoblasts [61].

## 5. Zinc and RANKL/RANK/OPG in bone

The aim of this study was to review the effect of zinc on RANKL/RANK/OPG pathway in the skeleton. In a recent animal study, zinc supplementation in ovariectomized (OVX) and diabetic (T1DM) rats resulted in increases in OPG expression that led to marked decreases in RANKL/OPG ratio [93]. Another study indicated zinc antioxidant property might prevent RANKL/RANK/OPG disbalance in Cd-induced rats [94], whilst an in vitro study on mouse marrow cells indicated that adding zinc sulfate led to inhibition in RANKL-induced osteoclast-like cells [95]. Additionally, zinc sulfate could increase OPG mRNA expression after 24–48 h in cultured cells, based on an in-vitro study [96]. The reports of a study regarding the effects of zinc demonstrated that as a result of using a zinc-free diet, the expression of RANK reduced and the level of RANKL and OPG did not change. Overall [97], indicated that zinc deficiency could decrease both osteoclastogenesis and osteoblastogenesis [97]. The result of an in vitro investigation regarding M-CSF and RANKL highlighted that zinc can prevent osteoclasts differentiation by the dose-depending reduction in RANKL [98]. In a recent study, the effects of Puerarin and zinc on ovariectomized rat (OVX) bones demonstrated co-supplementation decreased RANKL and increased OPG and OPN (osteopontin) [99]. It was further demonstrated that RANKL worked through indirect $Ca2+$ signaling mediation [100]. Based on a rat study, adequate consumption of zinc likely does not affect osteoblastogenesis, but it may reduce osteoclastogenesis via suppression of RANK expression through prevention of ROS (reactive oxygen species) production and ERK (extracellular signal-regulated kinase) activation [101]. A recent study has shown, in the group of mice in the TNF inflammatory environment, with a higher concentration on Zn, RANKL expression is meaningfully diminished [102]. The effect of zinc supplementation on diabetic induced bone loss has been investigated through an animal study, demonstrating that supplementation can reduce chronic T1DM-induced bone loss by increasing OC (osteocalcin) and decreasing RANKL and OPG [103]. Also, another experiment on diabetic rat demonstrated a reduction in RANK expression via zinc supplementation [104]. In Fong et al, a higher ratio of RANKL/OPG was reported in a metallothionein knockout (MT -/-) group and received a lower amount of zinc compared to others [105]; whilst, according to Liang et al, zinc could affect OPG gene expression in osteoblasts and increasing it [106].

**Table 1**
Summary of the reviewed studies, describing the effects of Zn on RANKL/RANK/OPG pathway in skeleton. RANK (receptor activator of Nf-kB), RANKL (receptor activator of NF-kB ligand), OPG (osteoprotegerin) and OVX (ovariectomized), STZ (streptozotocine).

| Intervention | Time | Species | Outcome | Reference |
|---|---|---|---|---|
| Zinc supplement | 90 days | OVX/T1DM rats | ↓ RANKL/OPG | [93] |
| Zinc supplement | 6 months | Cadmium induced male rats | ↓ sRANKL<br>↓ RANKL/OPG | [94] |
| Zinc sulfate | 7 days | Mouse marrow cells (in vitro) | ↓ RANKL | [95] |
| Zinc sulfate | 3 days | Osteoblastic cells (in vitro) | ↑ OPG | [96] |
| Zinc deficiency | 3 weeks | Female rats | ↓ RANK | [97] |
| zinc | 4 days | Mice (in vitro) | ↓ RANKL | [98] |
| Zinc + puerarin | 12 weeks | OVX rats | ↓ RANKL<br>↑ OPG | [99] |
| zinc | 1 week | Female rats | ↓ RANK | [101] |
| zinc | 3s days | Mice osteoblasts cell (in vitro/inflammatory condition) | ↓ RANKL | [102] |
| Zinc supplement | 90 days | Diabetic male rats | ↓ RANKL<br>↓ OPG | [103] |
| Zinc supplement | 1 week | Diabetic rats (STZ-induced) | ↓RANK | [104] |
| zinc | 2 days | Osteoblastic cells (in vitro) | ↑ OPG | [106] |
| Zinc supplement | 4 weeks | Male rats | ↑ RANKL | [107] |
| ZIP4 suppression | – | Mouse (pancreatic cancer) | ↓ RANKL | [108] |
| Zinc-modified titanium | 28 days | Human stem cells (in vitro) | No change in OPG<br>RANKL | [109] |

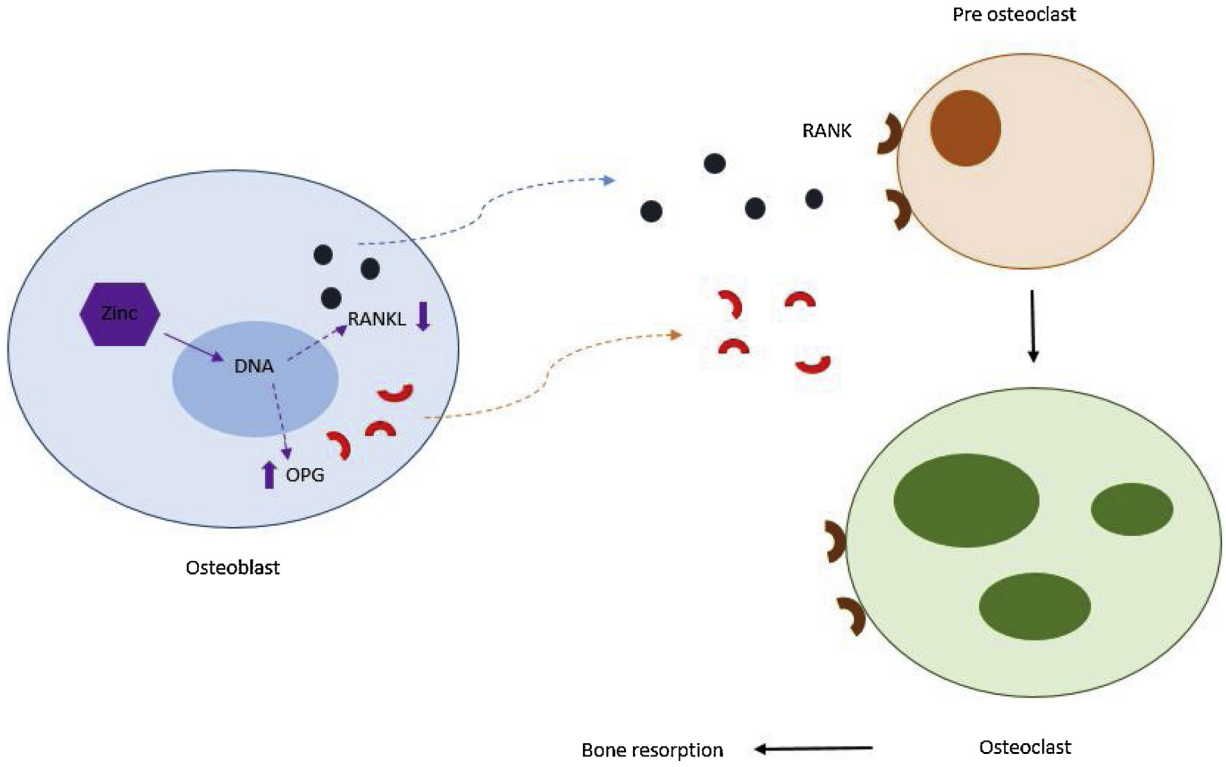


**Fig. 1.** Binding between RANKL and RANK lead to maturation in osteoclasts and enhance bone resorption. OPG, as RANKL decoy receptor, would prevent of RANKL/RANK binding and down-regulating bone loss. Most of the studies have reviewed, indicated a significant reduction in RANKL and increment in OPG. RANKL (receptor activator of NF-kB ligand), RANK (receptor activator of NF-kB), OPG (osteoprotegerin).

In contrast to these studies, there are some studies which show distinct consequences. In a study on male rats that received zinc supplements, it was reported that dietary zinc supplementation upregulated RANKL expression in bone by TNF-α and IL-1β; this resulted in bone loss without any specific change in the size of bones [107]. It was shown in another animal study that suppressing ZIP4 (Zinc transporter ZIP4) could up-regulate bone mineral density and down-regulate bone turnover in mice with pancreatic cancer via RANKL-RANK system [108]; whilst some work has reported that zinc-modified titanium (EZ) affects osteoblasts differentiation but no significant changes in OPG and RANKL levels are observed [109] (Table 1) (Fig. 1).

## 6. Conclusion

In conclusion, it is likely that sufficient zinc intake will elicit positive effects on bone health by RANKL/RANK/OPG regulation. Although the outcomes of a few studies are equivocal, it seems that zinc can exert the protective properties against bone loss by suppressing osteoclastogenesis via downregulation of RANKL/RANK. Additionally, there are several experiments where zinc supplementation resulted in upregulation of OPG expression. However, the results of limited studies oppose this. Therefore, aside from the positive role zinc possesses in preserving bone mass, further effects of zinc in RANKL/RANK/OPG system

requires further animal/human studies.

## Declaration of Competing Interest

The authors declare no conflict of interest regarding the present article.

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